EpiDex® Swiss field trial 2004-2008

Ortega-Zilic, N ; Hunziker, T ; Läuchli, S ; Mayer, D ; Huber, C ; Baumann Conzett, K ; Sippel, K ; Borradori, L ; French, L E ; Hafner, J

Abstract: BACKGROUND: Approximately 20% of leg ulcers remain unresponsive to the best conservative standard of care. So far, these patients could either receive conventional skin grafts or had to accept their intractable wound. Skin substitutes from cell culture may represent a promising alternative to heal a major part of these patients on a non-surgical, potentially more cost-effective basis. OBJECTIVE: To systematically evaluate the first 68 patients treated in Switzerland (Swiss EpiDex® field trial 2004-2008). METHODS: Retrospective study on EpiDex treatment of a complete consecutive series of 68 patients with chronic wounds (66 chronic leg ulcers, 2 sores) unresponsive to best conservative standard of care. The primary end point was complete wound closure within 9 months after transplantation, the secondary end points change of wound surface area, pain reduction and overall judgement by the patient. Adverse effects were infection, dermatitis and others. Calculation of treatment costs was made. RESULTS: By the end of the study, 50/68 (74%) of patients had their wound completely healed [venous 29/37 (78%); mixed 7/9 (78%); others 14/22 (64%)]; 10/68 (15%) had the wound surface area reduced by >50%, and 8/68 (12%) did not respond to the EpiDex treatment. Wound pain disappeared completely in 78% and partially in 13%. Fifteen patients (22%) received antibiotics for wound infection, and 2 (3%) developed dermatitis (not related to the local therapy). Average treatment costs for venous ulcers amounted to EUR 5,357, compared to EUR 5,722-8,622 reimbursed according to the German DRG system (2010) for an in-patient skin graft. CONCLUSION: EpiDex may effectively heal up to three quarters of recalcitrant chronic leg ulcers. Thus, it represents an intermediate step to avoid costly in-patient split-skin mesh graft treatments. Patients remain mobilized, and a donor site is avoided. Large wound size or a necrotic wound bed limit the use of EpiDex. Otherwise, it offers the opportunity to avoid conventional skin grafts in a significant number of chronic leg ulcer patients. Copyright © 2010 S. Karger AG, Basel.

DOI: https://doi.org/10.1159/000321333

Original Paper

Dermatology

Dermatology 2010;221:365–372
DOI: 10.1159/000321333

Received: May 2, 2010
Accepted after revision: September 14, 2010
Published online: November 11, 2010

EpiDex® Swiss Field Trial 2004–2008

Natalie Ortega-Zilic[a] Thomas Hunziker[c] Severin Läuchli[a] Dieter O. Mayer[b]
Clarissa Huber[a] Katrin Baumann Conzett[a] Kirstin Sippel[a] Luca Borradori[c]
Lars E. French[a] Jürg Hafner[a]

Departments of [a]Dermatology and [b]Cardiovascular Surgery, University Hospital of Zürich, Zürich, and
[c]Department of Dermatology, University Hospital (Inselspital), Berne, Switzerland

Key Words
EpiDex® · Skin substitute, autologous · Epidermal equivalent · Plucked anagen hairs · Outer root sheath keratinocytes · Cell culture · Wound healing · Leg ulcer · Venous ulcer · Field trial · Unselected consecutive case series

Abstract
Background: Approximately 20% of leg ulcers remain unresponsive to the best conservative standard of care. So far, these patients could either receive conventional skin grafts or had to accept their intractable wound. Skin substitutes from cell culture may represent a promising alternative to heal a major part of these patients on a non-surgical, potentially more cost-effective basis. ***Objective:*** To systematically evaluate the first 68 patients treated in Switzerland (Swiss EpiDex® field trial 2004–2008). ***Methods:*** Retrospective study on EpiDex treatment of a complete consecutive series of 68 patients with chronic wounds (66 chronic leg ulcers, 2 sores) unresponsive to best conservative standard of care. The primary end point was complete wound closure within 9 months after transplantation, the secondary end points change of wound surface area, pain reduction and overall judgement by the patient. Adverse effects were infection, dermatitis and others. Calculation of treatment costs was made. ***Results:*** By the end of the study, 50/68 (74%) of patients had their wound completely healed [venous 29/37 (78%); mixed 7/9 (78%); others 14/22 (64%)]; 10/68 (15%) had the wound surface area reduced by >50%, and 8/68 (12%) did not respond to the EpiDex treatment. Wound pain disappeared completely in 78% and partially in 13%. Fifteen patients (22%) received antibiotics for wound infection, and 2 (3%) developed dermatitis (not related to the local therapy). Average treatment costs for venous ulcers amounted to EUR 5,357, compared to EUR 5,722–8,622 reimbursed according to the German DRG system (2010) for an in-patient skin graft. ***Conclusion:*** EpiDex may effectively heal up to three quarters of recalcitrant chronic leg ulcers. Thus, it represents an intermediate step to avoid costly in-patient split-skin mesh graft treatments. Patients remain mobilized, and a donor site is avoided. Large wound size or a necrotic wound bed limit the use of EpiDex. Otherwise, it offers the opportunity to avoid conventional skin grafts in a significant number of chronic leg ulcer patients.

Background

Leg ulcers represent a frequent and costly medicosocial problem [1–8]. They considerably impair the quality of life [9–11] and usually require 3–6 months to heal in 60–80% of patients, with approximately 20% remaining refractory

EpiDex is an acronym for an autologous epidermal equivalent of outer root sheath keratinocytes from plucked anagen hairs.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1018–8665/10/2214–0365$26.00/0

Accessible online at:
www.karger.com/drm

Prof. Jürg Hafner, MD
Department of Dermatology
University Hospital of Zürich
CH–8091 Zürich (Switzerland)
Tel. +41 44 255 25 33, Fax +41 44 255 89 88, E-Mail juerg.hafner@usz.ch

to all conservative medical measures [12–17]. Skin substitutes derived from cell culture systems [18] have, therefore, been developed and proposed for the use in the latter, difficult-to-heal leg ulcer patients, also with the goal to reduce the need for expensive in-patient skin grafts [19–22].

Over the past 30 years, since Rheinwald and Green [23] published their technique to cultivate keratinocyte autografts, many phase II and some phase III trials with cultured, autologous or allogeneic epidermal or epidermodermal skin substitutes have been conducted all over the world, with the two major aims to treat extensive burns or chronic wounds [18]. In Switzerland, two skin substitutes are commercially available for the treatment of difficult-to-heal leg ulcers: (a) Apligraf® [24] (Organogenesis, Mass., USA) and (b) EpiDex® [25] (Euroderm, Leipzig, Germany). Both products have proven their effectiveness in randomized controlled trials, Apligraf versus best standard of care and EpiDex versus split-skin grafting. Apligraf has been available in Switzerland from 1999 to 2002, and was reintroduced in 2008. EpiDex became commercially available in 2004; however, until 2008 it was reimbursed on request only. Therefore, only a limited number of 68 patients were treated with this product during 2004–2008.

By August 2008, Swiss regulatory authorities had approved both products for reimbursement by the common health insurance, provided that a chronic wound does not improve with the optimal standard of care for at least 3 months. The users are instructed and certified by the Swiss Association of Wound Care in collaboration with the Swiss Society of Dermatology and Venereology.

Objective

The current, retrospective study was conducted to systematically evaluate effectiveness, safety, impact on wound pain and costs during the Swiss field trial from January 2004 to July 2008, including all 68 consecutive patients who underwent grafting of EpiDex during this period of time.

Patients and Methods

The study was submitted to and approved by the Ethics Committee of the Canton of Zürich.

Patients

The retrospective, multicentre cohort study (field study) comprised all 68 chronic wound patients (66 leg ulcers, 2 sores) who were treated in Switzerland during the period from January 2004 to July 2008 (table 1). The 7 involved centres were: Department of Dermatology, University Hospital of Zürich (n = 36), Regional Hospital Le Sentier, Vallée de Joux (n = 8), Department of Dermatology, University Hospital of Bern (n = 6), Department of Surgery, Cantonal Hospital of Luzern (n = 3), Department of Dermatology, University Hospital of Basel (n = 2), Department of Dermatology, Cantonal Hospital of St. Gallen (n = 2), Department of Angiology, Regional Hospital of Thun (n = 2), plus 9 wound centres or private offices each of which treated 1 patient. The complete patient data sets were collected and analysed at the Department of Dermatology at the University Hospital Zürich. Five patients had died by the end of data acquisition. In all 5 cases, the relatives consented to the evaluation.

To qualify for the EpiDex procedure, patients had to present with a chronic leg ulcer of any main aetiology that failed to reduce its size for longer than 3 months despite thorough diagnosis and correction of all contributing factors, particularly despite adequate compression treatment for chronic venous insufficiency, saphenectomy in cases with isolated superficial venous reflux, revascularization in patients with refractory mixed ulcers and an ankle-brachial pressure index below 0.75 or in patients with arterial leg ulcers, repeated debridement of necrotic tissue and biofilm layers when required and systemic antibiotic treatment in cases of wound infection.

Clinical Procedure

Negative HIV, hepatitis B and C serology is a prerequisite for inclusion, as required for the safety of the cell culture laboratory. Depending on the size of the wound, 70–350 (70/10 cm^2 wound surface area) anagen hairs are plucked using a forceps, mainly from the supra-auricular scalp. Optimally, plucking should be performed from Monday to Wednesday so that the outer root sheath keratinocytes arrive at the laboratory before Friday noon. The laboratory requires approximately 7–10 days to culture a primary keratinocyte culture and another 14–18 days to grow the organotypic epidermal discs of 1 cm in diameter ready for grafting (fig. 1). Remarkably, in contrast to interfollicular keratinocytes, the proliferative potential of outer root sheath keratinocytes, which contain pluripotent adult stem cells, does not depend on the age of the donors. EpiDex is then delivered on a refrigerated agar soaked with transport medium in units of six 1-cm discs, according to the wound area. The epidermal discs are reinforced with a silicone carrier membrane. Thursday and Friday are optimal days for delivery. Before application, wounds are cleansed once more from all necrotic tissue, fibrin layers and biofilms. The EpiDex discs are placed in direct contact with the wound, the basal cell layer facing the granulation tissue and the silicone membrane lying on top so that they evenly cover about 50–70% of the wound bed (fig. 2a, b). The grafting procedure itself is painless and does not require anaesthesia. Most clinicians familiar with the method recommend to cover the grafted wound with adhesive foam (fig. 2c) and cotton gauze wraps. As an alternative, we have found a paraffin gauze covered with saline-soaked sterile cotton gauze a particularly convenient dressing, a technique derived from conventional surgical skin grafting (fig. 2d). Compression treatment is applied if required to treat underlying venous disease or other forms of leg oedema. The first change of dressings is performed on days 3–5 after grafting. It must be conducted with the utmost care, leaving

Table 1. EpiDex Swiss Field Study 2004–2008: aetiologies of treated wounds

Aetiology	Number of patients treated with EpiDex
Venous leg ulcers	37 (54%)
Mixed venous-arterial leg ulcers	9 (13%)
Martorell's hypertensive ischaemic leg ulcer	3 (6%)
Klinefelter's syndrome and leg ulcer	3 (6%)
Rheumatoid arthritis and venous disorder (leg)	2 (4%)
Systemic sclerosis and venous disorder (leg)	1 (2%)
Arthrogenic (stiff ankle joint)	2 (4%)
Arterial leg ulcer (non-Martorell)	2 (4%)
Adult progeria (Werner's syndrome)	1 (2%)
Pyoderma gangraenosum under immunosuppression (leg)	1 (2%)
Antiphospholipid syndrome (primary; foot)	1 (2%)
Livedo with summer ulceration (non-antiphospholipid; leg)	1 (2%)
Infectious non-healing under antibiotics (leg)	1 (2%)
Postsurgical chronic wounds on the leg	1 (2%)
Dermatitis artefacta of the leg	1 (2%)
Sore in paraplegia (1 heel, 1 sacral)	2 (4%)
Total	68 (100%)

the silicone protective membranes untouched (fig. 2e), as the EpiDex discs can easily be damaged or torn off during the initial phases of wound healing. Initially, the EpiDex discs may be barely visible, but when upon air exposure keratinization is enhanced with time, they become more apparent. Therefore, up to 30 min of air drying is recommended during every change of dressings, which is commonly scheduled twice per week. After 4–6 weeks, a second delivery of EpiDex is available on request, with the usual delay of 14–18 days to cultivate the organotypic secondary culture from the cryopreserved cells of the primary culture (fig. 3).

Evaluation of Treatment Results

Primary End Point. The monthly rate of completely healed wounds until 9 months after the first EpiDex transplantation was counted on an intent-to-treat base.

Secondary End Points. Change of wound size was evaluated in non-healed ulcers. Patients with a wound size reduction >50% were reported as partial responders. Pain relief and overall treatment satisfaction were scored by the patients using 4 quality levels: 0 = no improvement or deterioration; 1 = moderate improvement; 2 = marked improvement; 3 = problem resolved.

Adverse Effects. Infection at the recipient site, increase in wound size, increase in pain and major discomfort during hair plucking were systematically recorded. Moreover, patients were encouraged to report any further drawbacks of the whole procedure.

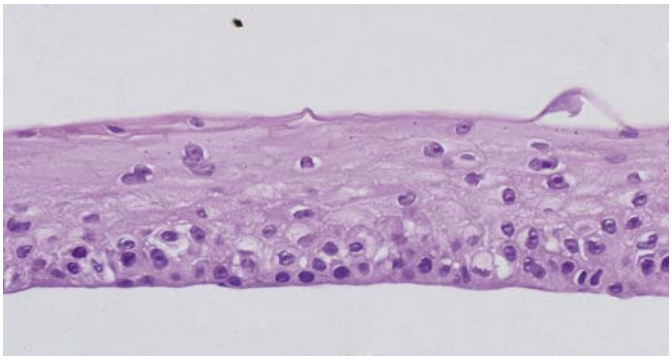

Fig. 1. Histology of EpiDex shows the living autologous epidermal equivalent with its physiological stratification (basal cell layer, squamous cell layer, faint horn layer).

Calculation of Treatment Costs

The calculation of treatment costs was composed by the skin substitute itself and medical care. The cost of EpiDex amounted to CHF 3,000 (EUR 2,160; USD 2,880) for small wounds (6 discs of 1 cm diameter), CHF 4,500 (EUR 3,240; USD 4,320) for medium size wounds (9 discs of 1 cm diameter) and CHF 6000 (EUR 4,320; USD 5,760) for larger wounds (12 discs of 1 cm diameter) (money exchange from August 6, 2010: 1 CHF ~ 0.72 EUR; 1 CHF ~ 0.96 USD). In 1 particular case, a wound care centre ordered 21 discs at the cost of CHF 10,500. Monthly costs of medical care were calculated at CHF 600 (EUR 432; USD 576) all included, i.e. personnel (physicians and nurses) and material (dressings and bandages). Calculation of treatment costs ended with complete wound healing [e.g. 6 units of EpiDex and 3 months for complete wound closure = CHF 3,000 + 1,800 (EUR 2,175 + 1,296; USD 2,880 + 1,728)] or at the latest at 9 months, regardless of the treatment outcome.

Results

Patients

The study included 68 patients with chronic wounds (66 leg ulcers, 2 sores) unresponsive to the best conservative standard of care. The median age was 75 years (mean 70.3, SD ±17.8, range 24–99). The female-to-male ratio was 35:23. The aetiology of chronic skin ulceration is summarized in table 1. Two thirds of included patients (68%) had chronic venous or mixed venous-arterial ulcers. The mean wound surface area was 17.0 cm^2, SD ± 19 cm^2 and range 1–100 cm^2.

Treatment Results

By the end of the study, 50/68 (74%) of patients had their wound completely healed [venous 29/37 (78%); mixed 7/9 (78%); others 14/22 (64%)]; 10/68 (15%) had the

Fig. 2. a The EpiDex discs are placed in direct contact with the wound, the basal cell layer facing the granulation tissue and the silicone membrane lying on top. **b** The discs should evenly cover about 50–70% of the wound bed. **c** Most commonly used initial bandage: a thin foam. **d** Alternative initial bandage: paraffin gauze (underlying) covered with a layer of saline-soaked sterile cotton wool. **e** Silicone protective membranes left in place during dressing changes.

wound surface area reduced by >50% (partial response); 8/68 (12%) did not respond to the EpiDex treatment (fig. 4).

Complete remission of wound pain was reported by 53/68 patients (78%). All of them had completely or almost completely healed wounds at the end of the study. In 9 patients (13%) wound pain was improved, and 1 patient (2%) did not experience any improvement of wound pain at all. Data on wound pain were missing in 5 patients. Overall judgement reflected largely the success in wound closure and pain reduction, i.e. 52 patients (76%) reported their problem to be completely solved, and an-

Fig. 3. a Chronic venous leg ulcer at first visit (same as fig. 2a–d): dry fibrin layer and necrosis, no granulation tissue, no epithelization. **b** Response to first EpiDex transplantation: epithelization at the top half of the wound area, vital granulation tissue at the bottom, second transplantation ongoing (week 8). **c** After the second EpiDex transplantation (week 9). **d** Complete epithelization (week 13).

other 6 (9%) reported substantial improvement. In total, 58 (85%) would repeat the procedure, if necessary.

Hair plucking caused so little discomfort as not to be mentioned by 52 patients (76%), and 11 (16%) felt the pain to be only mild (no data in 5 patients).

Adverse Reactions

Wound infection was the most frequent adverse reaction during the whole treatment. Fifteen patients (22%) received systemic antibiotic therapy for wound infection or critical colonization, amongst them 8 patients (12%) in the first week following the last EpiDex application.

Two patients (3%) had leg eczema around their wound, probably due to maceration and venous stasis. Both had no contact to potentially allergenic dressings (exclusively paraffin gauze and moist cotton wool on top of EpiDex).

Treatment Costs

The average treatment costs are summarized in table 2.

Discussion

As yet, this is the largest field trial on the use of EpiDex in chronic wounds, particularly hard-to-heal vascular leg ulcers. The results are in line with the first and only randomized controlled trial of the German-Swiss study group [25]. Approximately 3 in 4 leg ulcer patients can be healed using this innovative technique, on condition that the causative factors are identified and controlled and the wound bed is well prepared. Based on our experience, we meanwhile suggest small- to medium-sized chronic

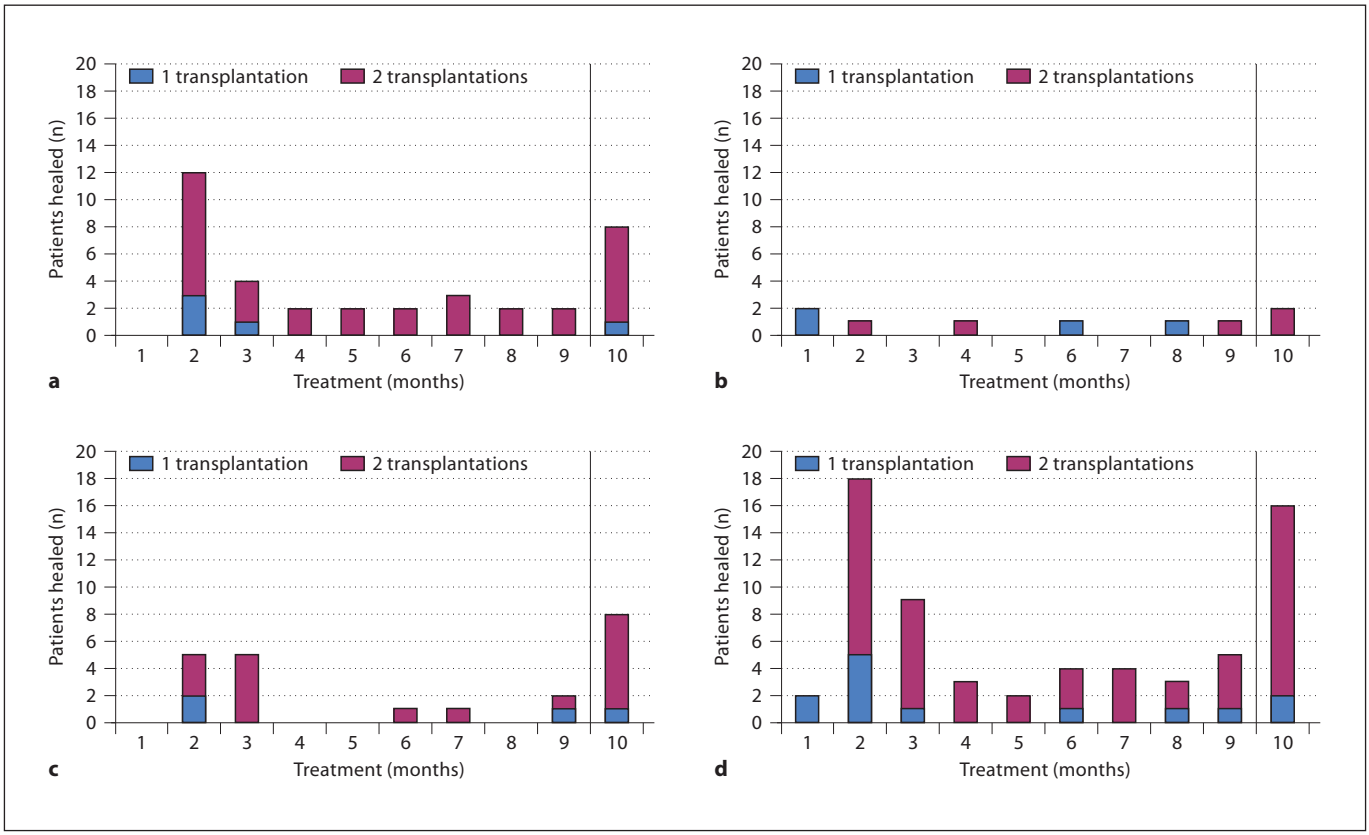

Fig. 4. Healing rates with EpiDex, according to aetiology and overall. **a** Venous ulcers: 29/37 healed (78%). **b** Mixed venous-arterial ulcers: 7/9 healed (78%). **c** Other types of chronic leg ulcers: 14/22 healed (64%). **d** Total of treated leg ulcers: 50/68 healed (74%).

Table 2. Calculated treatment costs of the EpiDex procedure

	CHF	EUR	USD
Venous leg ulcers (n = 37)	7,427 (4,200–14,700)	5,347 (3,024–10,584)	7,130 (4,032–14,112)
Mixed venous-arterial leg ulcers (n = 9)	10,267 (3,600–17,100)	7,392 (2,592–12,312)	9,856 (3,456–16,416)
Other leg ulcers (n = 20) and sores (n = 2)	7,391 (4,200–12,900)	5,322 (3,024–9,288)	7,095 (4,032–12,384)
All EpiDex cases (n = 68)	7,791 (3,600–17,100)	5,610 (2,592–12,312)	7,479 (3,456–16,416)

For details of calculation, see text.

wounds of any aetiology that show suitable granulation tissue, but lack epithelization, to be a valuable indication for the use of EpiDex. We acknowledge that the impressive results of our study have to be partially attributed to a positive patient selection. Very large (e.g. semicircular or circular leg ulcers) or totally necrotic wounds (e.g. acute necrotic vasculitis or Martorell hypertensive ischaemic leg ulcer during progressive breakdown) are unsuitable for this type of treatment, and such patients have not been treated with EpiDex during our observation period.

Approximately 20% of chronic leg ulcers fail to heal under the best standard of care [12–17]. Traditionally, wounds not responding to the best conservative standard of care either have to be accepted as intractable or to be

repaired surgically, typically with a split-skin mesh graft [19–22]. EpiDex as a living epidermal equivalent seems to represent an intermediate solution. If 20/100 leg ulcer patients remain intractable, EpiDex may be capable to heal – at most – another 15 of these 20 refractory leg ulcers. It is also noteworthy that it avoids expensive in-patient treatment, confinement to bed and the split-skin donor site.

To asses the cost-effectiveness of EpiDex in comparison with an in-patient split-skin graft, a variety of assumptions can be made, particularly depending on the medical insurance models of different countries. Based on US reports, but also on older reports from Switzerland, the use of EpiDex would be half as expensive as an in-patient treatment [reported to amount to CHF 12,000–18,000 (EUR 8,640–12,960; USD 11,520–17,280)] and exceptionally even more [21, 26]. But even when the more rigid scale of German DRGs (diagnosis-related groups) is used, EpiDex would still be 6–38% more cost-effective than an in-patient treatment. According to the G-DRG Version 2010 Definition Handbook [27], conservative in-patient treatment of a patient with a venous leg ulcer gets reimbursed with EUR 6,962.90 (DRG F21B), and surgical treatment of a patient with a venous ulcer of >4 cm^2 surface by tangential ablation and mesh grafting (shave therapy [19]) with EUR 8,621.70 (DRG F21A), calculated on an average base rate of EUR 2,900. The chapter for vascular diseases comprises the base DRG F21. In other cases, a chronic skin ulcer can also be calculated via the chapter for skin diseases, using the base DRG J02. In that case, surgical treatment of a chronic skin ulcer >4 cm^2 yields EUR 5,721.70 (DRG J02C).

Conclusions

EpiDex represents a valuable autologous epidermal equivalent to repair hard-to-heal chronic wounds, particularly chronic vascular leg ulcers. It is capable to heal up to three quarters of the 20% of leg ulcer patients who do not respond to the best standard of conservative wound care. EpiDex thus offers an intermediate solution for these patients, to eventually avoid costly in-patient split-skin graft treatments. Thereby, patients always remain mobilized, and there is no donor site wound. According to the authors' experience, EpiDex is particularly suitable for small- to medium-sized chronic wounds that show some granulation tissue, but fail to re-epithelialize.

Hopefully, the Swiss as well as European regulatory authorities will abstain from submitting this type of autologous keratinocyte transplantation to the criteria applied for the approval of pharmaceutical products. That type of reglementation must not be applied to the use of autologous grafting of skin cells, in which the biological markers and physiological functions of the cells are not altered or manipulated in any way. This would enable EpiDex to enter the European market, and then multicentre treatment registries could help to confirm the currently available data and to further outline the optimal indications.

Disclosure Statement

Thomas Hunziker developed EpiDex and owned the original patent which was spinned off and transferred to Mondex SA in 2003. All other authors declare no conflict of interest.

References

1 Ruckley CV, Evans CJ, Allan PL, Lee AJ, Fowkes FG: Chronic venous insufficiency: clinical and duplex correlations. The Edinburgh Vein Study of venous disorders in the general population. J Vasc Surg 2002;36:520–525.

2 Rabe E, Pannier-Fischer F: Bonner Venenstudie der Deutschen Gesellschaft für Phlebologie: epidemiologische Untersuchung zur Frage der Häufigkeit und Ausprägung von chronischen Venenkrankheiten in der städtischen und ländlichen Wohnbevölkerung. Phlebologie 2003;32:1–14.

3 Nelzén O, Bergqvist D, Lindhagen A: Long-term prognosis for patients with chronic leg ulcers: a prospective cohort study. Eur J Vasc Endovasc Surg 1997;13:500–508.

4 Moffatt CJ, Franks PJ, Doherty DC, Martin R, Blewett R, Ross F: Prevalence of leg ulceration in a London population. Q J Med 2004;97:431–437.

5 Ruckley CV: Socioeconomic impact of chronic venous insufficiency and leg ulcers. Angiology 1997;48:67–69.

6 Olin JW, Beusterien KM, Childs MB, Seavey C, McHugh L, Griffiths RI: Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. Vasc Med 1999;4:1–7.

7 Etufugh CN, Phillips TJ: Venous ulcers. Clin Dermatol 2007;25:121–130.

8 Ramelet AA, Perrin M, Kern P, Bounameaux H: Phlebology, ed 5. Issy-les-Moulineaux, Elsevier-Masson, 2008.

9 Hareendran A, Doll H, Wild DJ, Moffatt CJ, Musgrove E, Wheatley C, Franks PJ: The venous leg ulcer quality of life (VLU-QoL) questionnaire: development and psychometric validation. Wound Repair Regen 2007;15:465–473.

10 Herber OR, Schnepp W, Rieger MA: A systematic review on the impact of leg ulceration on patients' quality of life. Health Qual Life Outcomes 2007;5:44.

11 Klyscz T, Jünger M, Schanz S, Janz M, Rassner G, Kohnen R: Quality of life in chronic venous insufficiency (CVI): results of a study with the newly developed Tubingen Questionnaire for measuring quality of life of patients with chronic venous insufficiency. Hautarzt 1998;49:372–381.
12 Moffatt CJ, Franks PJ, Oldroyd M, Bosanquet N, Brown P, Greenhalgh RM, McCollum CN: Community clinics for leg ulcers and impact on healing. BMJ 1992;305:1389–1392.
13 Marston WA, Carlin RE, Passman MA: Farber MA, Keagy BA: Healing rates and cost efficacy of outpatient compression treatment for leg ulcers associated with venous insufficiency. J Vasc Surg 1999;30:491–498.
14 Humphreys ML, Stewart AH, Gohel MS, Taylor M, Whyman MR, Poskitt KR: Management of mixed arterial and venous leg ulcers. Br J Surg 2007;94:1104–1107.
15 Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, Taylor M, Usher J, Wakely C, Earnshaw JJ, Heather BP, Mitchell DC, Whyman MR, Poskitt KR: Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. Lancet 2004;363:1854–1859.
16 Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA: Dressings for healing venous leg ulcers. Cochrane Database Syst Rev 2006; 3:CD001103.
17 O'Meara S, Cullum NA, Nelson EA: Compression for venous leg ulcers. Cochrane Database Syst Rev 2009;1:CD000265.
18 Hunziker T, Limat A: Cultured keratinocyte grafts. Curr Probl Dermatol 1999;27:57–64.
19 Schmeller W, Gaber Y, Gehl HB: Shave therapy is a simple, effective treatment of persistent venous leg ulcers. J Am Acad Dermatol 1998;39:232–238.
20 Tanner JC Jr, Vandeput J, Olley JF: The mesh skin graft. Plast Reconstr Surg 1964;34:287–292.
21 Turczynski R, Tarpila E.: Treatment of leg ulcers with split skin grafts: early and late results. Scand J Plast Reconstr Surg Hand Surg 1999;33:301–305.
22 Jones JE, Nelson EA: Skin grafting for venous leg ulcers Cochrane Database Syst Rev 2007;2:CD001737.
23 Rheinwald JG, Green H: Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. Cell 1975;6:331–343.
24 Falanga V, Margolis D, Alvarez O, Auletta M, Maggiacomo F, Altman M, Jensen J, Sabolinski M, Hardin-Young J: Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Study Group. Arch Dermatol 1998;134:293–300.
25 Tausche AK, Skaria M, Böhlen L, Liebold K, Hafner J, Friedlein H, Meurer M, Goedkoop RJ, Wollina U, Salomon D, Hunziker T: An autologous epidermal equivalent tissue-engineered from follicular outer root sheath keratinocytes is as effective as split-thickness skin autograft in recalcitrant vascular leg ulcers. Wound Repair Regen 2003;11: 248–252.
26 Küng EE, Panizzon R, Hafner J: Ulcus cruris – ein Fass ohne Boden? Retrospektive Datenerhebung zur Behandlung von Patienten mit Ulcus cruris venöser und gemischter Genese unter stationären Bedingungen von 1989 bis 1992. Phlebologie 1994; 63:34–40.
27 Institut für das Entgeltsystem im Krankenhaus: DRG F21 and J02; in InEK (eds): G-DRG German Diagnosis Related Groups Version 2010 Definition Handbook, Compact Version. Siegburg, InEK Publishers, 2009, vol 1, pp 379–385, and vol 2, pp 11–18. www.g-drg.de; www.dimdi.de.